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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/613,975	07/03/2003	Donald L. Wise	CSI 130	8618

23579 7590 05/18/2007

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EXAMINER	
SHAHNAN SHAH, KHATOL S	
ART UNIT	**PAPER NUMBER**
1645	

MAIL DATE	DELIVERY MODE
05/18/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/613,975	WISE ET AL.	
	Examiner	Art Unit	
	Khatol S. Shahnan-Shah	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 January 2007 and 08 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. In view of the appeal brief filed on January 01, 2007, PROSECUTION IS HEREBY REOPENED. New rejections are set forth below. To avoid abandonment of the application, appellant must exercise one of the following two options: (1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or, (2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid. A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:

Status of Claims

2. Applicants' amendment of 1/04/2007 has been acknowledged. Claim 9 has been amended by the applicants. Claims 1 and 3-11 are pending in this application and are under consideration.

Rejections Withdrawn

3. All previous rejections are withdrawn, new rejections are set forth below.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 3-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition (a mucoadhesive controlled released particulate delivery system) inducing immunogenic response against certain

pathogens (Malaria and Anthrax), does not reasonably provide enablement for a vaccine for inducing immune response against all pathogens as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP) 2164.01(a). Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples (6) the quantity of experimentation, (7) the relative skill of those in the art, and (8) the breadth of the claims.

In the instant case claims 1, 3-11 are very broad and drawn to a vaccine. The only given example in the specification is in pages 11 and 14, mentioning the production of antigens for certain species of malaria and anthrax. When a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated base on that limitation. See in re Vaeck, 947 F. 2d 488, 495,20 USPQ 2d 1438, 1444 (Fed Cir, 1991).

Dorland's Medical Dictionary (29th Edition, 2000) defines "vaccine" as "a suspension of attenuated or killed microorganisms (bacteria, viruses, or rickettsiae), or of antigenic proteins derived from them, administered for the **prevention, amelioration, or treatment of infectious diseases**. In the instant case the applicants' invention is not enabled for the **prevention, amelioration, or treatment of all infectious diseases**. And one skilled in the art will not be able to make/and or use the invention without undue experimentation commensurate in scope with the claims.

Stedman's Medical Dictionary (27th Edition, 2000) defines pathogen any virus, microorganism (i.e. bacteria, parasites and fungi) or other substance causing disease. The term pathogen is very broad and can include any organism or substance disease causing in humans, animals, plants, fish etc.

The term inducing immune response is also broad and include preventive immune response, as well induced and innate immune response. The claims are very broad and drawn to a vaccine, which encompasses any pathogen. The specification fails to teach a skilled artisan how to administer the claimed composition for immune protection. The specification presents a paper protocol in this regard. The specification has not taught a skilled artisan how to use the invention as presently claimed. Applicants have not shown or disclosed a correlation between in vitro and in vivo studies or that there are animal models that correlate to human (i.e. person) efficacy. Applicants' specification fails to provide guidance to the skilled artisan on the parameters for DNA vaccine for the breadth of the claimed invention. Numerous factors complicate the DNA vaccine therapy art, which have not been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated. Attwood, T. K. (Science Vol. 290,) October 20, 2000) teach that to predict genes in uncharacterized DNA is unreliable, it is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences, and knowing the structure does not inherently tell us the function (see page 471). In the instant invention there is no correlation between structure and function. Additionally, the specification does not provide any working examples, which enable the claimed invention. Nor does the specification provide any guidance to the skilled artisan on how to make and use genetic (i.e. DNA) constructs of all pathogens, which would result in the desired effect (prevention and treating disease). Even assuming that an effective genetic material is constructed, it is not evident that DNA encode specific antigen to elicit immune response or to prevent disease. Therefore, even if the

specification enabled the construction of the delivery vehicle comprising malaria DNA in mice, in the absence of particular guidance, the artisan would have been required to develop *in vivo* and *ex vivo* means of practicing the claimed methods and such development in the nascent and unpredictable DNA vaccine art would have been considered to have necessitated undue experimentation on the part of the practitioner.

A disclosure in an application, to be complete, must contain such description and details as to enable any person skilled in the art or science to which it pertains to make and use the invention as of its filing date, In re Glass, 181 USPQ 31; 492 F2.d 1228 (CCPA 1974). While the prior art setting may be mentioned in general terms, the essential novelty, the essence of the invention, must be described in such details, including proportions and techniques where necessary, as to enable those persons skilled in the art to make and utilize the invention. For example applicants argue that prior art shows that DNA vaccines are considered to be enabled and as evidence give reference to Pachuk et al. (Current Opinion in Molecular Therapy Vol. 2, No. 2, 2000, prior art of record, applicants' Form 1449). It is the examiner's position that the same reference, page 188 recites " DNA vaccine technology, however, is still in its infancy and much research needs to be done to improve the efficiency with which these vaccines work with humans" page 195 under conclusion the paper recites " It is recognized that one of the major limitations to the success of DNA vaccines is its delivery", (see Pachuk et al. page 195). Pachuk et al. recite that structure rational designs for DNA delivery are limited. In addition it is unclear as to which cell type should be targeted for DNA delivery for optimal elicitation of immune response (see page 188 right column, 2nd paragraph). McDonnel et al. of University of Michigan (Medscape General Medicine, Vol.1, No 3, 1999) summarize problems with DNA vaccines as following: There are many problems and unanswered questions concerning the use of DNA vaccines. The possibility of insertional mutagenesis is a concern that needs to more rigorously tested. While there is no evidence that the introduced DNA integrates into the host genome, if it were to occur, it would raise the specter of carcinogenesis; oncogensis may be turned on or tumor suppressor genes inhibited. What if DNA circulated throughout the body after delivery? Might subsequent generation express the

antigen from birth and develop tolerance instead of immunity to the pathogen? Anti-DNA antibody formation and the possibility of autoimmune disease is another concern (see page 4 of 6 The emerging Role of DNA Vaccines, Medscape). In conclusion the specification does not support the broad scope of the claims, which encompass recombinant forms and any isolated phages. Thus, applicant has **not** provided sufficient guidance to enable one of ordinary skill in the art to how to make and use the claimed invention in manner reasonably correlated with the scope of the broad claims.

In view of all of the above, in view of the lack of predictability in the art, it is determined that it would require undue experimentation to make and use the Invention commensurate in scope with the claims.

Applicants' arguments on a notice appeal submitted 01/08/2007 have been acknowledged. Applicants in pages 7-9 argue:

The present application is directed to compositions, which provide controlled release of DNA vaccines. The claims define encapsulating nucleic acid encoding an antigen eliciting an immune response to a pathogen in a mucoadhesive controlled release particulate formulation comprising an open-celled polymeric foam of approximately 95% void volume, or particles thereof DNA encoding antigen is encapsulated into a mucoadhesive controlled release particulate formulation to achieve sustained delivery of the vaccine and to maintain an immune response.

The specification clearly enables a skilled artisan to make and use the claimed vaccine formulation. The pathogens and antigens are known. The specification at least at page 11, lines .1-3 states that the antigen is a nuclei acid molecule encoding a protein that induces immunity. Suitable antigens are known and available from commercial, government and scientific sources (see the specification at least at page 11, lines 14-15). The claims are drawn to anew formulation providing a means for enhancing mucosal delivery of these nucleic acids encoding " known antigens. The claims are drawn to an improved DNA vaccine formulation generally, not a specific vaccine. Appellants do not claim to have invented DNA vaccines, and indeed have provided much evidence to show that DNA vaccines are known. The specification and application instead are drawn to the advantages obtained using the polymeric carrier. The best

evidence against the examiner's rejection is the article cited by the Examiner in the Office Action mailed December 22, 2003, O'Hagan, J. Pharm. Pharmacol. 50:1-10 (1997) ("O'Hagan"), a copy of which is enclosed in the Appendix, dated four years before the priority date of this application. O'Hagan makes clear that even as of 1997, nucleic acid racemes, while not being perfect and having some FDA issues, were effective and could be delivered using a polymeric carder. Additional papers were enclosed with the Amendment and Response filed August 10, 2004 to show that DNA vaccines are considered to be enabled and vaccination with them does not require "undue experimentation". See pachuk, et al. Curt Opin Mol Ther. 2(2):188-98 (April 2000); Barnes, et al. Curr Opin Mol Ther. 2000 Feb; 2(1): 87-93 (February 2000); and Watts and Kennedy Int. J. Parasitol. 29(8): 1149-63 (1999) ("Watts"), copies of which are enclosed in the Appendix. The Examiner pointed to Pachuk, page 188 wherein is stated that "DNA vaccine technology is still in its infancy and much research needs to be done to improve the efficiency with which these vaccines work in humans as rebuttal to Appellants use of Pachuk as evidence that DNA vaccines are enabled. Appellants respectfully draw the Examiners attention to the fact that Pachuk is not stating that research needs to be done for DNA vaccines to work, but to improve the efficiency with which they work which means that they do work. Also, the Examiner quoted from Pachuk at page 195, which states "it is recognized that one of the major limitations to the success of DNA vaccines is its delivery. This in fact is the problem the present application seeks to solve (see the specification at least from page 9, line 26until page 10, line 31). Also quoted by the Examiner was the sentence in Pachuk stating that 'it is unclear which cell are to be targeted for optimal eliciting of immune response" •(referencing Pachuk, page 188). The specification discusses the cells to be targeted at least at page 10, lines 19-31.

The examiner has provided no evidence whatsoever that this method would not work; only unsupported allegation based on the belief that "the claims are very broad" (page 3, August 7, 2006, in a statement identical to the previous office action).

In response to applicants' arguments in regard to analysis of references cited by the office and applicants concerning scope of enablement rejections, the office will clarify

for the record that the rejection is based on scope of enablement. The applicants are enabled for composition (a mucoadhesive controlled released particulate delivery system) inducing immunogenic response against certain pathogens (Malaria and Anthrax), does not reasonably provide enablement for a vaccine for inducing immune response against all pathogens as claimed. As mentioned above the claims specifically claim 1 is broadly drawn to any vaccine (i.e. prevention and treatment) for any pathogen (i.e. any virus, microorganism (i.e. bacteria, parasites and fungi) or other substance causing disease). In response to applicants' arguments that the pathogens and antigens are known Ellis, R.W. (Chapter 29 of " VACCINES" [Plotkin, S.A. et al. (eds) published by W.B. Saunders company (Philadelphia) in 1988 recites that It is well recognized in the art, that it is unclear whether an antigen(s) derived from a pathogen will elicit protective immunity, especially page 571, 2nd full paragraph] exemplifies this problem in the recitation that " The key to the problem (of vaccine development) is the identification of protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies.... And thus protect the host against attack by the pathogen". In response to Pachuk, page 188 wherein is stated that "DNA vaccine technology is still in its infancy and much research needs to be done to improve the efficiency with which these vaccines work in humans and applicants' rebuttal use of Pachuk as evidence that DNA vaccines are enabled. The office brings applicants attention to the fact that Pachuk is stating that research needs to be done for to improve the efficiency with which they work which means it is determined that it would require undue experimentation to make and use the Invention commensurate in scope with the claims.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

7. Claims 1, 3-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recited the limitation " a vaccine composition for inducing an immune response to a pathogen comprising a nucleic acid encoding an antigen eliciting an immune response to the pathogen encapsulated in a mucoadhesive controlled release particle " It is not clear if the pathogen it self is encapsulated in the particle or it is the DNA encoding a specific antigen in encapsulated in the particle. It is also not clear if the DNA encoding the antigen from a pathogen.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1, 3-5 and 8-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Hagan Derek (Journal of Pharmacy and Pharmacology, Vol. 50, No. 1, pp.1-10,

1998). Prior art of record. USPTO 892, 12 /22/2003 in view of Mikos et al. (US 6,689,608 B1).

The claims are drawn a vaccine composition for inducing an immune response to a pathogen comprising a nucleic acid encoding an antigen in a biodegradable polymer.

O'Hagan Derek teaches a vaccine composition for inducing an immune response to a pathogen comprising a nucleic acid encoding an antigen in a biodegradable polymer (see abstract). O'Hagan teaches poly (lactide-co-glycolide) a biodegradable polymer (page 6). O'Hagan teaches a variety of pathogens including malaria and *Helicobacter pylori* (see pages 2 and 3). O'Hagan teaches encapsulation (page 6), adjuvants (page 5) particulates less than 5 micron and greater than 10 micron (see page 6). O'Hagan teaches mucosal immunization including nasal and oral (page 4). O'Hagan does not specifically teach that the composition is mucoadhesive. However, O'Hagan teaches that mucosal administration of the vaccine, which enhances the effectiveness of the vaccine (see abstract). O'Hagan teaches all the limitations of claimed invention. Limitations such as mucoadhesiveness of the formulation will be an inherent property of a microparticle formulated for mucosal delivery. O'Hagan does not explicitly teach an opened –celled polymeric foam of approximately 95% void volume or a particle thereof.

Mikos et al. teach a polymeric matrix formed of poly (lactide-co-glycolide) a biodegradable polymer with a polymeric foam of approximately 95% void volume (see abstract, claims specially claim 1 and column 4).

It would have been *prima facie obvious* to one of ordinary skill in the art at the time the invention was made to combine the teachings of O'Hagan with the teachings of T Mikos et al. to obtain a vaccine composition for inducing an immune response to a pathogen comprising a nucleic acid encoding an antigen eliciting an immune response to the pathogen encapsulated in a mucoadhesive controlled release particle a mueoadbesive controlled release particle comprising an open-celled polymeric foam of approximmely 95% void volume, or particles tlhereof .

One of skilled in the art would have been motivated to use polymer of 95% void volume taught by Mikos et al. replacing biodegradable polymer to deliver immunogenic compositions. One of ordinary skill in the art would have been motivated by the teachings of O'Hagan that in delivery of antigens by biodegradable polymers including PLG the particle size shown to be an important factor affectiong immunigenicity (see O' Hagan page 6).

Conclusions

10. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Khatol Shahnan-Shah whose telephone number is 571-272-0863. The examiner can normally be reached on Mondays and Wednesdays from 12:30-6:30 PM and Thursdays from 12:30-4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffery Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER

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May 9, 2007